November / December 2024
#120

the Analytical Scientist®

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Could AI Ever Replace The Analytical Scientist?

Working closely with an ever-expanding network of experts helps keep our content relevant and engaging. And keeps artificial intelligence at bay, right?!

The last issue of the year is a time for festivities and reflections. As for the latter, I've been pondering the real value of The Analytical Scientist in an era of generative AI.

In reality, AI-generated content can be pretty good when sufficient scrutiny is applied. In seconds, it can produce a decent summary of a research paper, an overview of the main trends in a given field, or a collection of recent papers on a topic – if we are willing to forgive the occasional hallucination. Nevertheless, I would like to make a bold prediction: I do not think AI will ever supplant The Analytical Scientist.

As I see it, The Analytical Scientist is a reflection of you – the people behind the methods, technologies, and tools. Our role? First, to extract the insightful ideas and inspiring experiences rattling around in the minds of the key thinkers in the field, and then to deliver them to the wider community in a way that is coherent, digestible, and possibly even enjoyable. In the process, we may initiate new conversations and spark ideas that help move the field forward. Collaborating or even just conversing with a network of experts – big thanks, as always, to our wonderful contributors and advisors – helps guide the direction of our content. And that is irreplaceable.

As you browse this month's issue, including the stories of innovation (that's where the festivities come in!), I'd like you to think about whether The Analytical Scientist is still fulfilling its purpose. If you think we could help serve the community better, I'd love to hear from you.

James Strachan,
Editor

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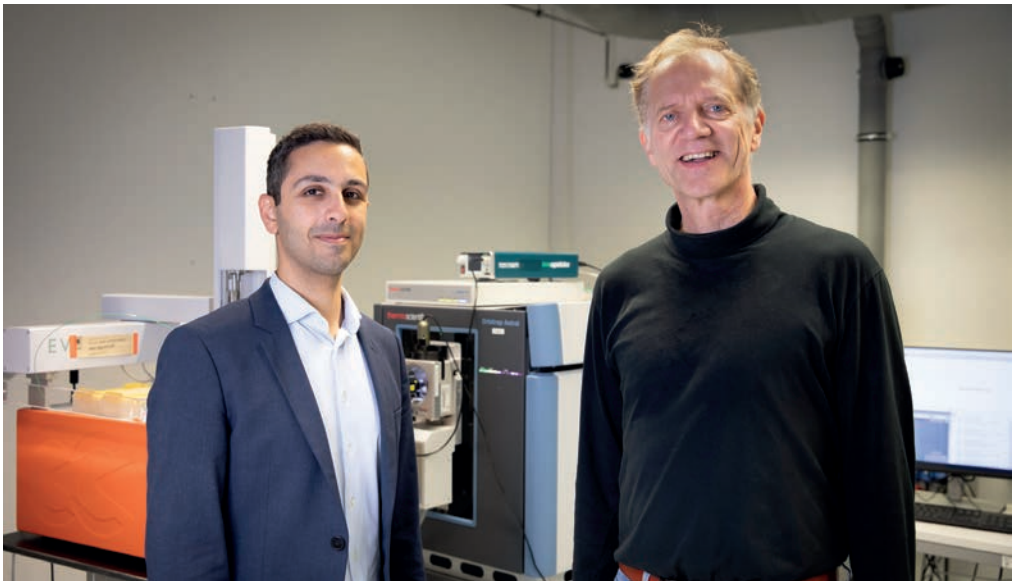
"A Turning Point in Translational Medicine"

Deep Visual Proteomics enabled Thierry Nordmann and his team to treat a previously untreatable skin condition



A breakthrough has been made in the treatment of the fatal skin condition toxic epidermal necrolysis (TEN), made possible through the use of a novel spatial proteomics technique.

In a recent study (1), researchers in a team led by Matthias Mann (Max Planck Institute of Biochemistry) used deep visual proteomics (DVP) to identify the hyperactivation of the inflammatory JAK/STAT pathway in keratinocytes and immune cells from patients suffering from TEN. This established JAK1 inhibitors as a potential treatment option which, when put in practice, resulted in the rapid re-epithelialization and recovery of affected cells in seven TEN patients.

The team applied DVP to formalin-fixed paraffin-embedded (FFPE) skin biopsies from both healthy patients and those suffering from mild to severe skin conditions, such as maculopapular rash (MPR) and TEN. Using AI and ultra-sensitive mass spectrometry, they were able to identify roughly 5,000 unique proteins in each cell type across their participants. From here they could study the disease-specific molecular mechanisms in each cell type under a range of conditions, leading to their eventual discovery.

To find out more, we spoke to first author Thierry Nordmann about the team's findings, and what he believes they could mean for the future.

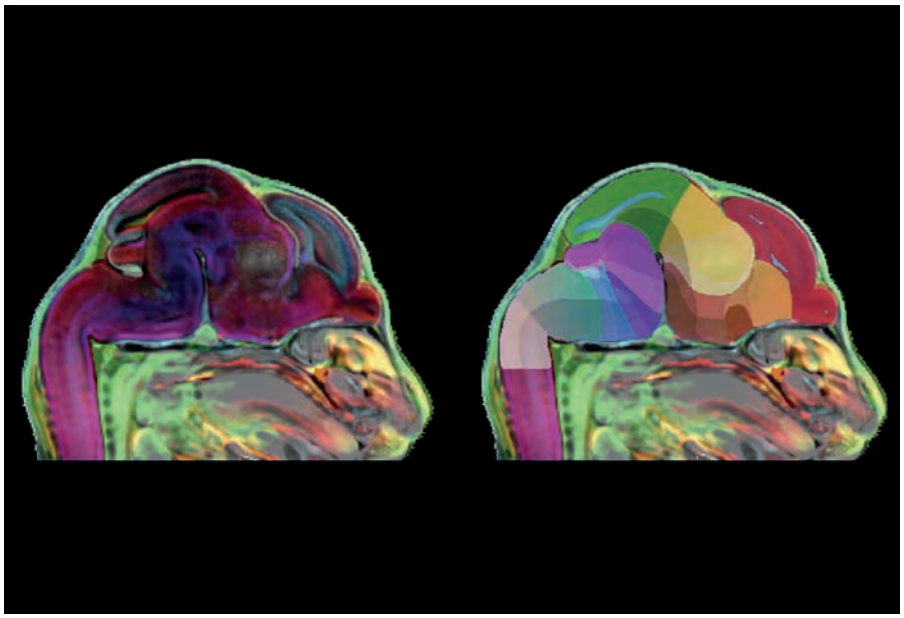
Please could you give us an overview of your spatial proteomics approach?
Deep Visual Proteomics (DVP) is a cutting-edge technology that combines microscopy, artificial intelligence, and ultra-sensitive mass spectrometry to analyze specific cell types directly from tissue sections. We applied this approach to study different types of cutaneous adverse drug reactions, ranging from mild maculopapular rash to severe and potentially fatal conditions like toxic epidermal necrolysis (TEN). The beauty of DVP is that it works with formalin-fixed paraffin-embedded (FFPE) tissue, allowing us to use archived diagnostic biopsies to build our patient cohort.

What was the biggest challenge you faced during the research?
One of our main challenges was studying such a rare disease as toxic epidermal necrolysis. DVP was a game-changer here because it allowed us to work with FFPE tissue sections, meaning we could build a cohort using retrospective cases from diagnostic biopsies. Laser microdissection of tiny immune cells located in the collagen-rich dermis was the next big challenge, but we managed to do so. Along the way, we even developed new standardized protocols for handling the specialized membrane slides needed for DVP.

Can you speak to the potential of spatial proteomics more broadly?
Spatial proteomics represents a powerful new way to understand disease mechanisms at molecular resolution. Our work shows how this technology can make a real difference. We were able to analyze thousands of proteins in specific cell types from archived patient samples, discover a key pathway driving disease, and translate this finding into successful treatment. This direct path from spatial molecular analysis to clinical impact is quite unique in the field of omics technologies. The ability to use archived tissue samples opens up entirely new possibilities – we can now study rare diseases where prospective sample collection would take years, or tackle fundamental questions about cellular aging at molecular resolution. I believe we are at a turning point in translational medicine, and we now have the right tools at the right time to fundamentally change how we understand health and treat diseases.

Reference

1. *T.M. Nordmann et al., Nature, 620, 123 (2024). DOI: 10.1038/s41586-024-08061-0.*



3D Atlas of the Developing Brain

A 3D atlas of the developing mouse brain has been created by researchers at Penn State College of Medicine. The atlas represents a common reference framework for analyzing brain architecture in both normal and diseased states. The team employed magnetic resonance imaging (MRI) to capture the overall form and structure of the brain across seven developmental time points – from the embryonic period to the immediate postnatal stage. The researchers also used light sheet fluorescence microscopy (LSFM) to visualize the developing brain at single-cell resolution, enabling precise mapping of brain cells and structures. By integrating these two imaging techniques, the researchers created a unified 3D framework – the Developmental Common Coordinate Framework (DevCCF).

Reference: F.N. Kronman et al., Nat Commun, 15, 9072 (2024).
Credit: Kim Lab / Penn State

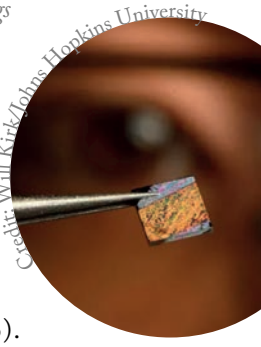
QUOTE *of the month*

"If I have learned anything, it's that you can push your limits so much further than you ever thought possible when you love what you do. But it is essential to keep your cool and persevere when the going gets tough. Of course, starting a new company can seem just like a triathlon at times…"

Sandra Pankow (see page 26)

SERS Chip Diagnoses Heart Attacks in Five Minutes

New metasurface-based blood test detects cardiac biomarkers in just minutes, offering faster diagnosis in clinical settings



Credit: Will Kirk/Johns Hopkins University

A new blood test (1) can diagnose heart attacks in 5–7 minutes using a plasmonic metasurface and surface-enhanced Raman spectroscopy (SERS). Developed by researchers at Johns Hopkins University, the test is significantly faster than current methods, which can take hours, detecting key cardiac biomarkers that signal a heart attack – and hopefully improving the chances for timely medical intervention.

The heart of this invention is a metasurface-enhanced chip that amplifies the signals used in SERS to detect trace levels of biomarkers, such as creatine kinase-myocardial band (CK-MB), myoglobin (Mb), and cardiac troponin-I (cTnI). These proteins are crucial indicators of heart attacks, but traditional diagnostic tests can take an hour or longer to detect them.

By employing a nanostructured metasurface, the system boosts both electric and magnetic fields in Raman spectroscopy, improving the detection of these biomarkers in real time. The metasurface enables higher sensitivity to biomarker signals even at ultra-low concentrations.

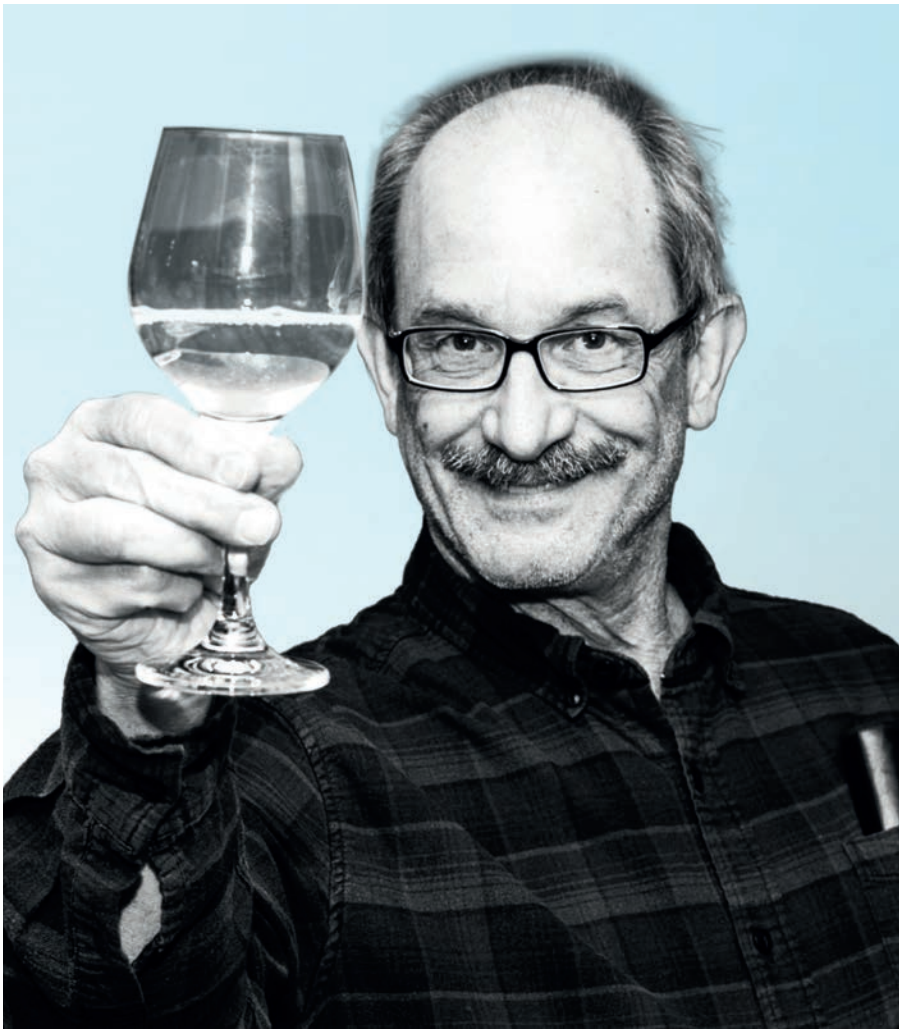
Reference

1. *P. Zheng et al., Adv Sci, 11, 202405910 (2024). DOI: 10.1002/advs.202405910.*

How to Succeed in Commercial Innovation

Sell your story, stay alert, be careful who you hire, and focus intensely on execution

By Lloyd Smith, W. L. Hubbell Professor of Chemistry, Department of Chemistry, University of Wisconsin – Madison, USA



As a scientist who has some success on the commercial front (I co-founded Third Wave Technologies, which commercialized molecular diagnostic products and went public in 2001), I have learned several lessons about commercial innovation, which I'd like to share.

First of all, the hard lessons. When I started as a Director, my attitude was pretty relaxed – thinking everything would be fine, and I'd just go to meetings, enjoy the dinners, sign off on things, and then leave. But as things happened in the company, I realized I wasn't alert enough to the issues or sufficiently proactive in taking action. It's a big responsibility, especially with a public company, and it deserves more than just passive involvement.

People used to tell me I was great at taking risks, and I'd accept the compliment. But I didn't actually see much risk at the beginning. We started with money we could afford to lose, so for me, it was just fun – if it worked, great, and if not, it didn't matter because I still had my day job. But once the company began to have real value, the risk became tangible. Now, with a stake in the company's worth, I had something to lose, and that made me more conservative in decision-making.

Another big thing I learned was the importance of people. I tend to assume the best in people – I try to behave well, so I expect others to behave well. But during the company's development, we had some issues with people we hired, and they ended up having a destructive effect on the company. That taught me to be more careful and aware when working with people in that environment. It's more of a life lesson, really – realizing that sometimes my model of projecting myself onto others doesn't work.

Then there were the challenges to my perspective – what you can and can't claim in a business environment. My friend, who ran the company, was more business-minded, while our other co-founder and I were all about the science. When he was out raising money, he would sometimes say things we didn't feel were completely accurate, and we'd get really uptight, telling him, "You can't say that; it's not true." Eventually, he lost his temper and said, "It doesn't matter if it's not possible today. It's our vision for the future, and we need to tell it to raise money. Then we'll hire the best people in the world, and we're going to make it work."

It was a jaw-dropping moment for me – a totally different way of thinking. But his approach worked exactly as he said. We raised a lot of money, hired top talent, did incredibly innovative work, and developed a valuable new platform technology. His ability to take a big-picture approach and raise funds based

"Eventually, he lost his temper and said, 'It doesn't matter if it's not possible today. It's our vision for the future, and we need to tell it to raise money. Then we'll hire the best people in the world, and we're going to make it work.'"

on vision was a huge factor in the company's success, and I'm still grateful to him for teaching me that lesson.

Another key lesson was the importance of focus, which I learned from Kevin Conroy, who came in as the CEO. Kevin went on to found Exact Sciences, the company behind the Cologuard test.

I remember us being really excited about our first product: we called it the CFLP (Cleavase-fragment length polymorphism) assay. It was our first commercial deal with Boehringer Mannheim, and they put it in their catalog. But it ended up being a complete flop. We had built up all this excitement around it, but it just wasn't viable.

When Kevin came on board much later, he did something I never would have done: focus all of the company's resources on a single goal – a single clinical trial for one specific test. That clinical trial ended up succeeding, the test got FDA approval, and the company was acquired for a significant amount of money. He's done the same thing with Exact Sciences, which is part of why they're so successful.

I often read about these stories where a company raises a ton of money, burns through it, but struggles because they don't have a focused product or their initial products fail. Their stock price plummets, and they're forced to reposition – to double down on one specific thing, hoping it will help them rise from the ashes. There's a phoenix metaphor in there somewhere…

Third Wave is an interesting case study because people often say that academics don't usually make the best CEOs – and it's somewhat true. We may be ideal for a stage of a company where big vision and expansion are key – where you need to get people excited, raise money, and create momentum. But when it comes to the execution stage – developing products that are valuable and marketable – it takes a different approach, one that's all about focus and discipline.

the Analytical Scientist

INNOVATION *Awards*

Meet the products – and the experts – defining analytical innovation in 2024

10 LiCellMo
(Live Cell Metabolic Analyzer)

Laboratory instrument allowing researchers to visualize changes in cell metabolism in real time

Produced by the Biomedical Division of PHC Corporation, a member of PHC Group

LiCellMo offers real-time visualization of metabolic changes in cell cultures, giving researchers a comprehensive view of cell activity. Unlike traditional methods that rely on periodic sampling – prone to contamination and gaps in data – LiCellMo provides continuous minute-by-minute measurements of glucose and lactate levels.

Insights from the LiCellMo team

"We believe that continuous monitoring will lead to more effective cell and gene therapy processes."

"The in-line monitoring technology featured in LiCellMo builds on proprietary technology from a blood glucose monitoring sensor developed by another part of PHC Group, the In Vitro Diagnostics (IVD) Division. The breakthrough for LiCellMo was when we realized we could use this BGM technology from the IVD business to develop a sensor for monitoring culture media."

What the judges say…
"Simply cool technology in cell monitoring!"

15 – 11

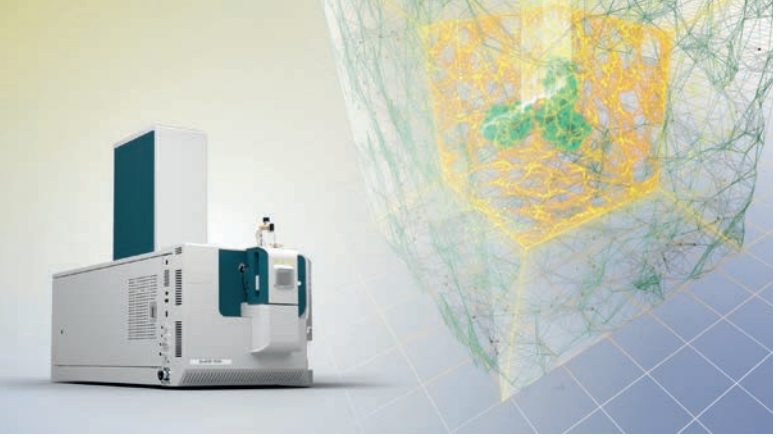
15 BEAM
The first dedicated single-point spectrometer – "unleashing the full power of FT-NIR spectroscopy"
Produced by Bruker Corporation

14 EVOQ DART-TQ+
Chromatography-free triple-quadrupole mass spectrometry for point-of-need routine analysis
Produced by Bruker Corporation

13 Vericheck ddPCR Replication Competent Kits (Lentivirus and AAV)
Quick and cost-effective solutions for the absolute quantification of replication competent lentivirus and AAV genes
Produced by Bio-Rad Laboratories

12 Pegasus BTX
The smallest and most sensitive GC-TOFMS on the market
Produced by LECO

11 Agilent ProteoAnalyzer System
Automated parallel capillary electrophoresis system for protein analysis
Produced by Agilent Technologies



9 ZT Scan DIA

Next-gen data-independent acquisition for quantitative proteomics

Produced by SCIEX

Building on SCIEX's established workflows, such as SWATH DIA and Zeno SWATH DIA, this new approach provides the comprehensive coverage DIA is known for while delivering enhanced precision, sensitivity, and selectivity characteristic of targeted quantitative workflows. In a nutshell, the ZT Scan DIA offers the ability to quantify more proteins with greater accuracy, bridging the gap between protein identification and translational applications.

Insights from Chief Research Scientist Steve Tate
"This drive to move proteomics into clinical cohorts, and understand critical biological questions, is resulting in extremely large sample sets. Given traditional LC/MS methods, where it would take 1 hour to identify and quantify 10,000 samples, ZT Scan DIA can analyze it in a fraction of the time, which will drive more biological insight and understanding of disease."

8 Echo MS+ System

Expanding high-throughput screening with acoustic ejection mass spectrometry

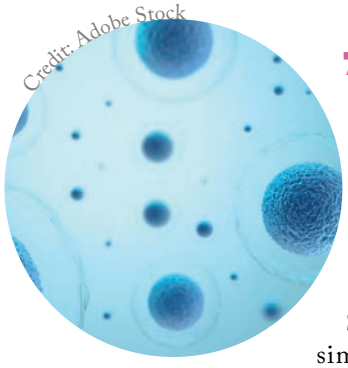
Produced by SCIEX

The Echo MS+ system integrates Acoustic Ejection Mass Spectrometry (AEMS) technology and Open Port Interface (OPI) sampling with the capabilities of the SCIEX ZenoTOF 7600 or Triple Quad 6500+ systems. This combination enables high-quality qualitative and quantitative results across a wide range of high-throughput screening workflows.

Insights from the Echo MS+ Team
"The Echo MS+ system expands the use of the mass spectrometry by addressing throughput limitations that have historically constrained its application in critical workflows," says Jose Castro-Perez, Vice President, Product Management at SCIEX.

"One memorable moment was the first successful demonstration of in-situ kinetics, allowing real-time analysis of reactions as they occur," says Chang Liu, Staff Research Scientist at SCIEX.

What the judges say…
"An important addition to those performing high-throughput clinical studies using MS."


Credit: Adobe Stock

7 ScalePlex

Multiplexing technology for large-scale single-cell omics

Produced by Scale Biosciences

ScalePlex enables the simultaneous analysis of over 300 samples, conditions, or time points – far exceeding the limits of traditional single-cell sequencing methods, which typically process only 12 samples at a time. Powered by Scale Bio's Quantum Barcoding technology, the workflow adds an oligo tagging step during fixation, avoiding the limitations of lipid- or antibody-based tagging. This streamlined process eliminates individual fixation and washing steps, preserving small or valuable samples often used in oncology and neuroscience research.

Insights from co-founder Frank Steemers

"ScalePlex technology enables experimental flexibility from small to large scale, multi-sample, multi-condition studies at single cell resolution."

"The 'aha moment' came when we discovered that oligonucleotides simply attach to nuclei or cells during fixation. We realized we could leverage this functionality as a sample barcode for single cell profiling."

6 Syft Explorer

The world's first fully mobile, real-time, and direct trace gas analyzer

Produced by Syft Technologies

The Syft Explorer enables real-time trace gas analysis with its portable mobile trolley design. With a runtime of up to 1.5 hours, this mobile mass spectrometer detects volatile organic compounds (VOCs) and inorganic compounds directly at the point of interest. Designed for contamination control engineers, researchers, production technicians, and environmental engineers, the Syft Explorer provides rapid analysis of airborne molecular contaminants, industrial pollutants, and toxic compounds at their source.

Insights from product management head William Pelet

"The Syft AMC Explorer is the only fully mobile, real-time and direct trace gas analyzer capable of monitoring almost any volatile compound."

5 Pyxis

A simple, scalable AI-powered platform for untargeted absolute quantitation of analytes

Produced by Matterworks, Inc.

Matterworks is taking powerful AI techniques developed for language and image processing and applying them to LC-MS data – enabling the direct transformation of uninterpreted, raw LC-MS data to a biologically actionable list of the identities and concentrations of detected metabolites. Pyxis standardizes the entire process of untargeted analyte quantitation – eliminating the need for per-analyte calibration, peak selection, integration, and manual data analysis.

Insights from CEO and co-founder Jack Geremia

"We see the potential to more than double the success rate of life-science pipeline R&D."

"Our eureka moment was realizing that molecular data, the most powerful data for explaining and predicting complex emergent biology, are already acquired at sufficient scale to enable a fundamental shift in how we perform life-science R&D."

"My innovation philosophy is to identify large unmet needs where there is an almost obvious technical solution, just that it doesn't yet quite exist."

4 Thermo Scientific Stellar MS

Completing a key piece of the translational research workflow by verifying new biomarker discoveries

Produced by Thermo Fisher Scientific

The Stellar mass spectrometer quantifies nearly 10,000 peptides per hour and offers four times higher sample throughput, significantly improving the speed and scale of biomarker translation from discovery to validation. Its advanced data acquisition capabilities enable robust, reproducible quantitation across a wide range of analytes and molecular classes, supporting extended dynamic range studies.

Insights from the Stellar MS Team

"Tools like the Stellar MS can expedite verification of biomarkers, making a substantial impact on future healthcare by improving lab productivity today," says product manager Cristina Jacob.

"It demonstrated that a simpler MS instrument could outperform high-end instruments in certain scenarios, particularly where speed and sensitivity were more crucial than very high mass accuracy and resolution," says senior scientist Philip Remes.

What the judges say…

"A brighter future for high-resolution, high-content MS and its high-throughput applications."

3 OptoVolt Module

A multiphoton microscopy module that enables millisecond neural event imaging at single neuron resolution

Produced by Bruker Corporation

OptoVolt enables imaging at over 1000 frames per second, capturing millisecond-scale neural communication dynamics. Optimized for fluorescent voltage indicators, it offers the temporal precision and signal-to-noise ratio required to detect individual neural events. When combined with Bruker's NeuraLight 3D Ultra spatial light modulator, OptoVolt allows researchers to explore neural input-output relationships with exceptional temporal and spatial resolution, advancing the study of complex neural networks.

Insights from the Stellar MS Team

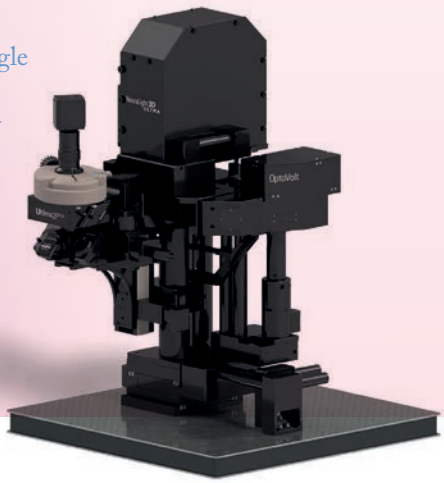
"The hope is that this module will allow neuroscientists to study neural communication with a temporal resolution, which has been difficult in the past."

"Much of the credit goes to the inventors of the core technology at Boston University and the collaboration and licensing of the technique crucial to the development of our imaging system."

What the judges say…

"Characterization of single neurons – an important step to enable organ-on-chip and cell single analysis."

"A breakthrough in neurological measurement technology."



2 Depixus MAGNA One

The world's first commercial technology for exploring single molecule interactomics at scale

Produced by Depixus SAS

The Depixus MAGNA One uses magnetic force spectroscopy (MFS) to measure binding forces, conformational changes, and kinetics at the individual molecule level, scaling to thousands of interactions in parallel. Unlike static or bulk-average techniques, it delivers direct, dynamic data on DNA, RNA, proteins, and small molecules, offering new insights into molecular heterogeneity and rare biological events.

Insights from co-founder and CEO Gordon Hamilton
"Our key innovation is combining the analytical power and precision of MFS with advances in imaging technology. Each individual pixel of a camera can be used to independently track the real-time dynamics of a single molecular interaction occurring directly above it, opening the door to massive scalability."

"We believe that MAGNA One's ability to see biology in action at the level of individual molecular interactions will transform the field of interactomics in the same way that single cell sequencing has transformed genomics."

What the judges say…
"New leap in the measurement of bio-molecular interactions."

"Potential to provide key information at the molecular level for drug discovery."

---

1 EMILIE

The first infrared analyzer based on nanomechanical sensing for FTIR spectrometers

Produced by Invisible-Light Labs GmbH

EMILIE is a nanomechanical infrared analyzer combining nanoelectromechanical sensing (NEMS) with optomechanical infrared (IR) technology. Offering picogram-level sensitivity in the mid-to-far IR range, it provides a rapid, cost-efficient solution for analyzing nanoparticles and nanomaterials, such as ultrafine aerosols, nanoplastics, and nanopharmaceuticals.

Insights from the Invisible-Light Labs Team
"Nanomechanical infrared spectroscopy required equipment not available in the standard analytical scientist's laboratory, such as an infrared (IR) quantum cascade laser, a laser-Doppler vibrometer, and cleanroom-fabricated nanomechanical chips. The breakthrough was to make this very sophisticated technology widely accessible by making it compatible with existing FTIR spectrometers."

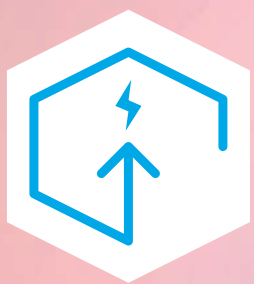
"With a picogram detection limit, EMILIE has the potential to play a crucial role in ensuring the safe and responsible use of nanomaterials and nanoparticles while providing valuable insights into their fundamental properties and behavior."

What the judges say…
"The EMILIE is a nanomechanical infrared analyzer that could help materials characterization with higher throughput and smaller samples."

"Innovative combination of two advanced technologies for nanomaterial characterization."

"Very innovative approach with high potential in miniaturized applications."

Credit: Romana Maalouf Photography



the Analytical Scientist

The INNOVATORS

Powering the Future of Analytical Science

Analytical science is in constant evolution; here, we present some of the newest innovations, pioneering software solutions, and technologies shaping the future of the field

Modern Software for the Analytical Lab

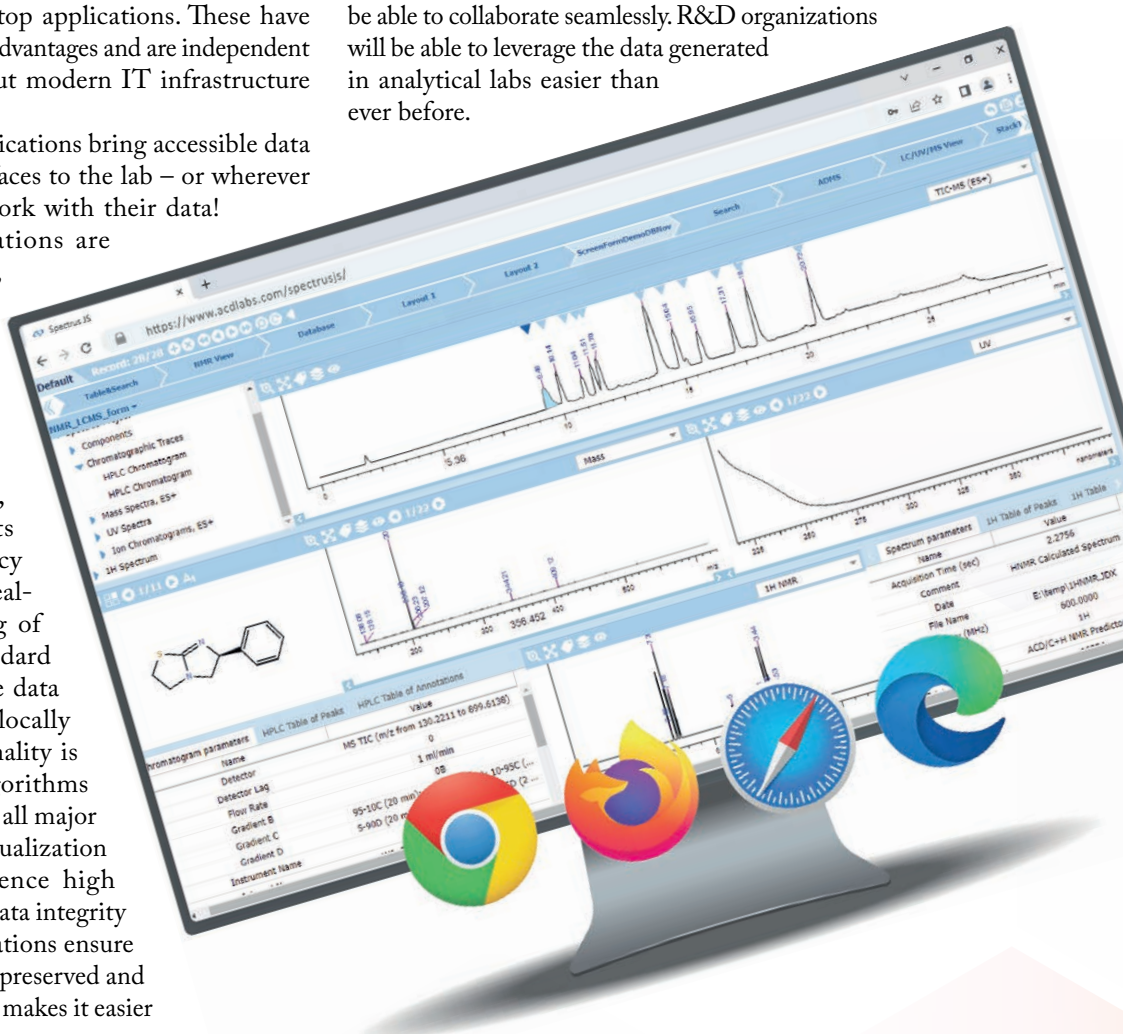
The Spectrus JS family brings the tools and capabilities scientists have long relied on and loved to the browser

The devices and apps we use in our personal lives have fundamentally changed our expectations of the software we use at work. Analytical chemistry software helps us extract answers from complex datasets to support decision-making and risk-management, provides proof for regulatory filings, fosters innovation through knowledge management and collaboration, and much more. While there has been a transition from software that's dedicated to the instrument, most analytical chemistry software is still limited to desktop applications. These have traditionally offered performance advantages and are independent from an internet connection, but modern IT infrastructure severely narrows this gap.

The Spectrus JS family of applications bring accessible data and modern user-friendly interfaces to the lab – or wherever scientists want to access and work with their data! The JavaScript-based applications are optimized for handling NMR, LC/UV/MS, and other analytical data along with chemical information. They leverage Spectrus Platform technology to render detailed chemical and analytical data in a web environment, bypassing platform constraints that typically accompany legacy software. Spectrus JS provides real-time interaction and reporting of complex datasets through standard web browsers. Users can explore data and process/reprocess without locally installed software. This functionality is achieved through advanced algorithms that convert analytical data from all major vendor formats for seamless visualization and interaction. Users experience high performance and precision with data integrity and traceability. Spectrus applications ensure that critical scientific insights are preserved and shared accurately. Spectrus JS also makes it easier for scientists and data scientists to collaborate seamlessly – an important factor in the modern R&D enterprise.

Spectrus JS is essential for the digital transformation of analytical labs. It provides simple deployment without download and installation on individual machines or networks; easy scalability, updates, and maintenance; and seamless integration with existing informatics systems via API. Spectrus JS facilitates data preparation, assembly, and validation, ensuring that analytical and contextual chemical data can be used in multi-platform environments and AI-enabled workflows. This is a critical need as data volumes and complexity grow. Furthermore, as R&D budgets and IT teams are stretched, web-based Spectrus JS enables the use of powerful, expert software on machines with low RAM and processing power.

As ACD/Labs continues to evolve its Spectrus software portfolio to web-based applications, analytical scientists will gain the freedom to work with their data with fewer restrictions and be able to collaborate seamlessly. R&D organizations will be able to leverage the data generated in analytical labs easier than ever before.



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Ask the Expert

Michel Klein Gunnewiek, Application engineer, Avantes

What was your route into analytical science?

I studied analytical chemistry at Saxion, before moving on to chemical engineering at the University of Twente. There, I focused on material science – a field I worked in for seven years before circling back to analytical science. Having a background in both materials science and analytical chemistry really helps me look at problems from different angles, which is certainly helpful in my current role at Avantes.

How does your company embody "innovation"?

At Avantes, we are constantly investing in R&D to improve our spectrometers and come up with new ways to make our devices work for different applications – whether it's making sensors more sensitive or making instruments smaller and more portable. We do this, driven by our company mission: to empower our customers to drive innovation forward in their area of expertise, with the help of our spectroscopy solutions.

What is the biggest innovation lesson you've learned over the last few years?

One big lesson is that innovation doesn't always mean huge breakthroughs. It also comes from small, steady improvements and learning from each version. Every time we change a design or get feedback on a new application, we learn something valuable. The little things add up over time, and it's important to keep that mindset of continuous learning.

What is your prediction for the future of analytical instrumentation?

I think analytical instrumentation is going to become even more integrated into everyday industrial and environmental processes. Instead of being limited to labs, I expect tools like spectrometers to be increasingly used in factories, farms, and other real-world settings, where they can provide instant data that helps optimize processes.

Illuminating the Pathway to Innovation

Use advanced triple detection to analyze the structure, shape, and conformation of polymers

The LenS3™ MALS-V detector is a dual detector for size exclusion chromatography (SEC) integrating multi-angle light scattering (MALS) and viscometry. Combined with the EcoSEC Elite GPC system and TSKgel columns, it offers a complete and cost-effective approach for triple detection analysis.

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Ask the Expert

Snežana Đorđević, Application Scientist, Analytical Instruments, Tosoh Bioscience

What was your route into analytical science?
With a background in pharmacy and analytical chemistry, I have dedicated my career to merging my skills into polymer characterization techniques. The possibility of producing something new, in a very creative way, with widespread application, is why I have chosen Application Scientist as the next role in my career. I am now dedicating my time to finding new applications of GPC in polymer characterization.

What motivates you?
My career path has trained me to ask questions, understand the answers, make conclusions, and provide solutions that will be useful not only to me but to my team and society. My multidisciplinary background has made me aware of how important it is to have a profound understanding of any analyte that requires characterization (including polymers), which can lead an analytical chemist to generate new ideas or optimize protocols.

How can innovation address some of the big challenges facing the field today?
We're seeing an increasing number of new polymer types, which are getting more difficult to characterize. Technology must keep pace with this rapidly growing field: we require innovation to improve detector sensitivity and versatility so that we may obtain accurate and reproducible data.

Do you have any innovation advice to share?
Trust your ideas, no matter how crazy they may sound, but also consult multidisciplinary experts to help you make those ideas reality.

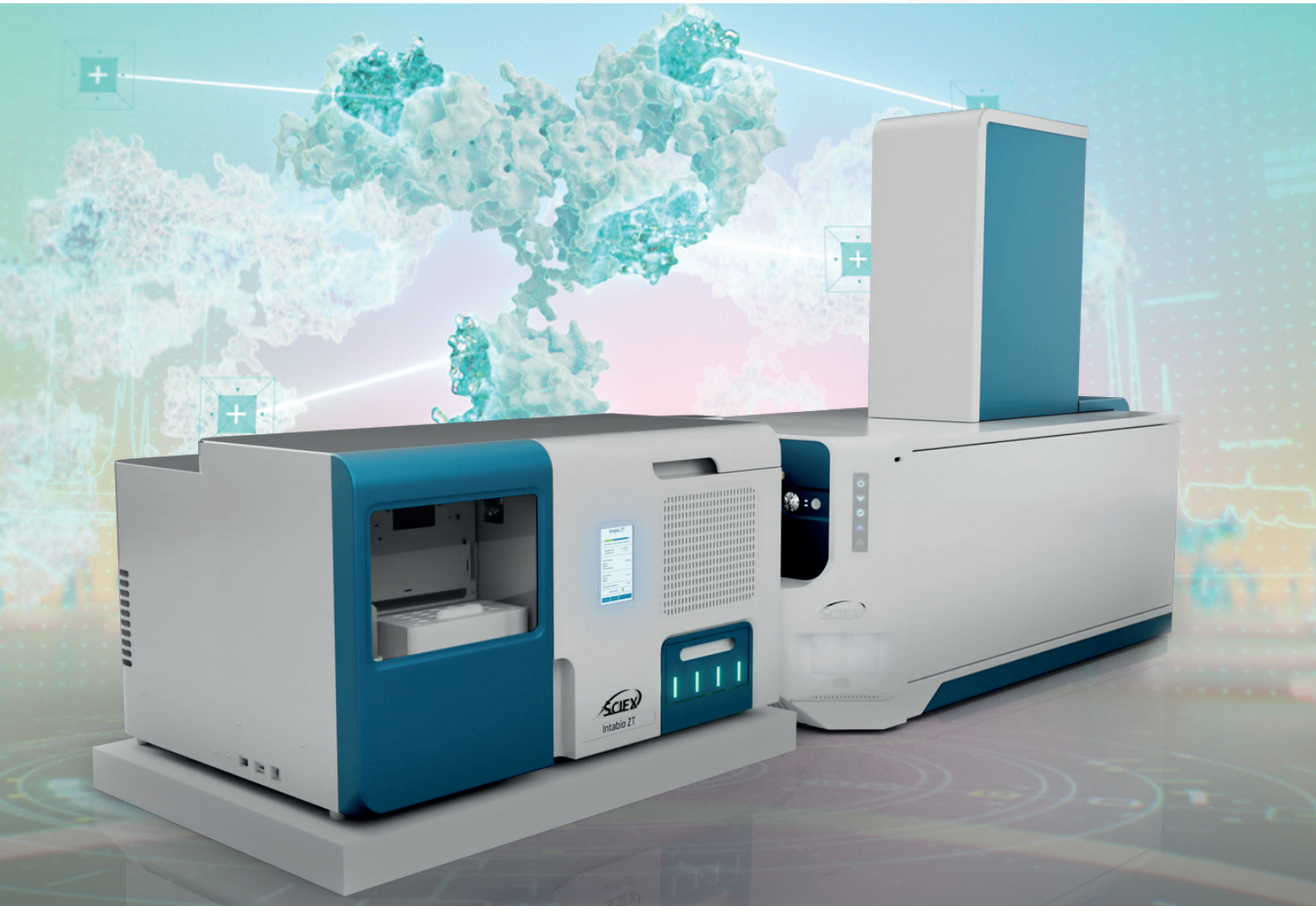
How important is collaboration to your innovation efforts? Any examples to share?
By collaborating with academics and companies we can share our expertise in SEC and help them answer their research questions; in return, they provide us with important feedback on our products – whether it be improving data analysis or column design.

SPONSORED FEATURE

Comprehensive Proteoform Identification in Minutes

The Intabio ZT system couples icIEF separation and UV detection with high-resolution mass spectrometry for peak identification

The process of identifying proteoforms in individual charge variant peaks and interpreting their structural differences conventionally takes weeks and requires the use of multiple instruments, with multiple steps. With the Intabio ZT system, separation, quantitation and identification of individual charge variants can be achieved in minutes on a single integrated platform.



Acquire charge variant separation profiles in minutes.

Support high throughput analysis with 15-minute separation and enable detailed characterization on charge variant peaks of multiple monoclonal antibodies without redundant method development or fraction collection.

Achieve highly confident critical quality attribute identification.

Identify common critical quality attributes (CQAs) like glycosylation, deamidation and glycation.

Identify proteoforms that could impact product quality.

Achieve high-resolution separation and identification of proteoforms with as little as 0.02 pI value difference.

Get the required information to make confident decisions, fast.

Maintain data continuity with a single workflow producing one, accessible dataset, where UV peaks correlate with MS peaks.

Learn more about the Intabio ZT system: SCIEX.com/IntabioZT

Ask The Expert

Scott Mack, Principal Scientist, SCIEX

What was your route into analytical science?
My first industrial post after graduating with a degree in Biochemistry was for an Assay Development and Implementation group supporting the testing of in silico-designed proteins. In the twenty years since then, I have expanded my research focus to include genomics, reagents, software, hardware and analytics.

How can innovation address some of the big challenges facing the field today?
When it comes to the development of biologic therapeutics, one of the greatest limitations is the current cost structure required to collect data and make informed decisions. The Intabio ZT system uses icIEF-UV/MS to radically reduce the resource intensity required for characterizing and identifying therapeutic proteoforms, allowing for unprecedented decision-making efficiency at every step in the product development lifecycle.

How important is collaboration to your innovation efforts? Any examples to share?
Collaboration is essential for innovation. The Intabio ZT system would not exist without the breakthrough contributions of at least a half dozen individuals. In my experience, members from the most innovative teams are looking to champion the best solutions rather than always promoting their own concepts.

What is your prediction for the future of analytical instrumentation?
I see the continued development of automation in instrument operation and analytics to reduce both researcher workloads and results variation. New instrument functionality and flexibility can be realized through the adaptation of microfluidic technologies, especially in the advancement of multidimensional analysis along with sample-to-result workflows.

MASS SPEC

The XCMS-METLIN Story

Gary Siuzdak's team at Scripps Research did more than just process LC/MS data – they mastered the art of distinguishing signal from noise, uncovering molecular identities hidden in the clutter of raw data

By Gary Siuzdak, Professor and Director at the Center for Metabolomics and Mass Spectrometry, The Scripps Research Institute, USA

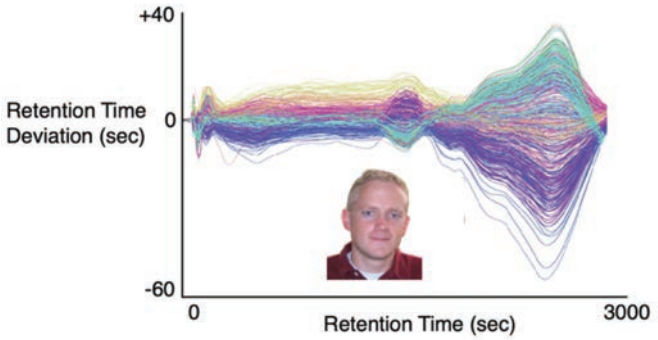


Figure 1. Derived from the first output from the XCMS program, retention time deviation versus retention time (Colin Smith inset), and what turned into the XCMS logo. (Analytical Chemistry, 2006)

The origins of The Analytical Scientist's 2023 Innovation Award-winning XCMS-METLIN platform trace back over three decades. The story begins in the early 1990s with a bold idea from Richard Lerner, then president of Scripps. Richard wanted to explore the cerebrospinal fluid of animals in a sleep-deprived state, looking for endogenous metabolites that might induce sleep. My task was to identify these molecules. We initially used GC-MS for the analyses, but this didn't give us the comprehensive data we needed.

That led to our first LC-MS-based metabolomic and lipidomic experiments, which culminated in several key publications (1,2). We discovered molecules correlating with the sleep-wake cycle, including one that induced a sleep-like state. But those early experiments were plagued by challenges. Data alignment and identification, in particular, posed significant barriers to progress. For example, retention time variability from run to run made it difficult to align data and discern real signals from noise. The complexity of molecular identification was another major hurdle, especially when manual methods were our only option.

The birth of XCMS – and nonlinear retention time alignment

The breakthrough came in the early 2000s when I challenged Colin Smith, a talented staff scientist, to improve our data analysis methods. The result? XCMS (3). XCMS introduced a novel concept: nonlinear alignment of LC/MS data. This allowed us to adjust for variations across experiments and vastly improved our ability to distinguish real signals from noise.

The first XCMS nonlinear correction plot (Figure 1) and algorithm, which addressed the challenge of LC/MS drift, has since become a widely emulated approach across the field. And given the large population of XCMS users, we are constantly listening to their thoughts on how XCMS can be improved. For example, pairwise analysis was always standard, however, the addition of XCMS single sample analysis and XCMS multi-group analysis came from user input.

Enter METLIN – the gold standard for molecular identification

Even with XCMS's alignment solutions, we still faced the challenge of identifying the myriad peaks from LC/MS data. Accurate mass measurements alone proved unreliable because isomers and isobaric compounds – like glucose, lactose, and fructose – share identical molecular weights. We needed something more.

That "something" was tandem mass spectrometry (MS/MS), which provides an additional level of molecular characterization. This realization led us to create METLIN – a comprehensive MS/MS database.

Initially, METLIN was built by collecting known endogenous metabolite and lipid standards, generating MS/MS data at multiple collision energies (0, 10, 20, and 40 eV). Over the first decade, METLIN cataloged over 10,000 molecules, growing to almost 20,000 in the second decade. Today, METLIN hosts MS/MS data on over 935,000 molecular standards from over 350 classes of molecules (Figure 2), this represents exponential growth made possible by solving three key challenges:

- Acquiring molecular standards: we gathered a vast range of molecules from over 350 chemical classes to populate METLIN, the acquisitions occurred from individual labs, chemical companies, and pharmaceutical firms. (Special thanks to Avanti Polar Lipids for the vast store of lipids they provided (Figure 3)).
- Automating data acquisition and maintaining data quality: high-throughput analysis capabilities emerged after a major lab flood in 2017 destroyed several of our instruments. Ironically, this disaster enabled us to rebuild with even better equipment and higher efficiency, translating into quality data generation during high throughput analyses (Figure 4).
- Informatics integration: Aries Aisporna, a key team member, deserves much credit for creating informatics solutions that allowed us to simultaneously process molecular information, guide the analyses, and integrate everything into a user-friendly platform.

Winnie Uritboonthai also played a critical role, optimizing our mass spectrometry systems

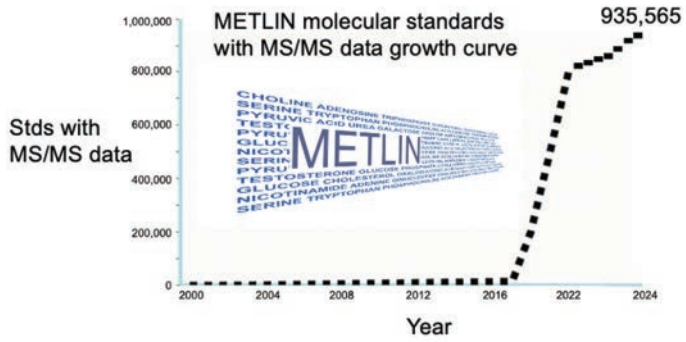


Figure 2. METLIN was created in the early 2000s initially with primary metabolites and lipids, and has since grown to contain over 935,000 molecular standards each with MS/MS data at multiple collisional energies. Therapeutic Drug Monitoring 2005, Nature Methods 2020, Mol. Sys. Biol. 2024

Figure 3. Pandemic era shipment of lipid molecular standards from Avanti Lipids; Winnie Urtiboonthai inspecting the delivery.

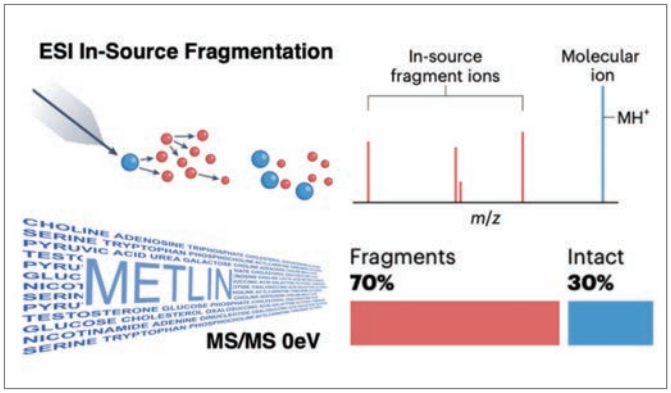


Figure 5. In-source fragmentation occurs when small molecules break apart within the mass spectrometer before mass analysis. This process, known since the early days of electron ionization, is also common with electrospray ionization (ESI). In ESI, fragment ions are generated and detected alongside intact molecules, adding complexity to LC/MS data. These fragments complicate interpretation because they represent portions of molecules rather than the entire entities, making it harder to determine the exact nature and quantities of substances in a sample. In-source fragmentation has long been a source of ambiguity in LC/MS data.

Figure 6. The integration of XCMS and METLIN as a local platform provides a streamlined means of LC/MS analysis and molecular identification, all within the confines of a personal computer.

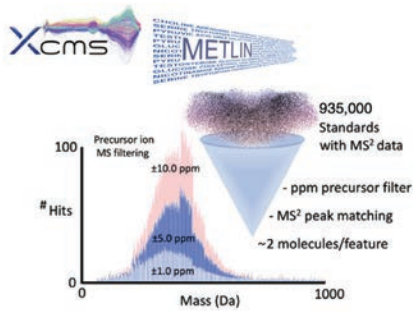


Figure 4. The flood of 2017 caught on video, filled the lab with 10,000 liters of water.

and processing over a million molecules with a success rate of around 80 percent. Thanks to her tireless efforts, METLIN has become the gold standard for MS/MS data, with experimental data for over 935,000 molecules at various collision energies.

XCMS-METLIN's impact – science and beyond

If I had to distill the real value of XCMS and METLIN, it would come down to their impact on science. These platforms have catalyzed key breakthroughs:

- XCMS: nonlinear alignment of LC/MS data (3)
- METLIN: streamlined molecular identification (4,5,6)
- Activity metabolomics: enabled by XCMS and METLIN (7,8,9,10)
- Phantom metabolites unveiled: an intriguing discovery from METLIN (Figure 5) is that much of the LC/MS data we once treated as meaningful is, in fact, noise – caused by in-source fragmentation (ISF). Through METLIN's unique acquisition of data at 0 eV, we have been able to distinguish true molecular ions from these fragments, simplifying our understanding of the metabolome and lipidome (11).

Beyond its scientific contributions, XCMS-METLIN has had significant commercial impact. Early cloud-based versions of XCMS have raised concerns about data privacy, especially for industry users. In response, our local version of the new XCMS-METLIN platform (Figure 6), allows companies and institutes to process their data in-house with the major added advantage of streamlined molecular identification with an unrivaled database.

But if there's one thing I've learned throughout the development of XCMS-METLIN, it's that no innovation happens in isolation. I've simply learned to listen and value the ideas of others – especially from brilliant scientists like Colin, Aries, and Winnie. XCMS-METLIN is the culmination of a tremendous team effort.

References avialable online

CHROMATOGRAPHY

Welcome to the Food Analysis Revolution

How developments in chromatography–mass spectrometry systems are enabling scientists to quantify the entire food aroma space in one run

By Hans-Gerd Janssen, Science Leader at Unilever Foods Innovation Centre; and Professor, Recognition-based Analytical Chemistry at Wageningen University, The Netherlands

Food flavor – i.e., the combination of taste and aroma – determines whether we appreciate a food product. Understanding flavor formation and flavor defects is, therefore, the number one research priority in the food industry. Indeed, every research project will have a flavor angle to it. To give a few examples: in the transition to plant-derived proteins we encounter bitterness issues; recycling packaging materials holds the risk of flavor transfer; and more sustainable, easier to recycle packaging materials generally have poorer barrier properties with more air and water reaching the packaged product; reducing temperatures in almond roasting to save energy; reducing salt and sugar levels to make a product healthier – these will all have flavor consequences. There is no change in raw material, production process, or packaging that comes without risks for the flavor of the food – and hence consumer appreciation.

However, flavor is very complex and far from fully understood. Whether or not you like a given food is a multisensory process, complemented with past associations, the subconscious, other aspects of psychology, marketing, and so on. Even if we focus exclusively on the chemistry – the interaction of molecules with receptors – it is complex. Compounds can have very different odor thresholds; two compounds together can have a smell completely different from that of the two individual species; response is highly non-linear; there can be masking issues…

And that is why the proof of the pudding will always remain in the eating! Taste panels are an indispensable tool in flavor research. They are often the only correct way to detect problems and quantify the extent of the issue. Panels describe what they taste and smell, analysis shows which compounds are present and for many compounds, odor descriptors are known. The direct combination of GC with human sniffing and MS, known as GC-MS-olfactometry (GC-O/MS), enables the identification of individual odorant molecules. However, GC-O/MS is a challenging technique and is typically considered a last resort when other methods are unsuccessful.

So, sensory paneling is here to stay. But human panels are notoriously inaccurate, subjective, and tremendously slow and expensive, which is why we need to minimize their usage.

Using analytical chemistry, we can identify the cause of a flavor and trace back its origin.

This is easier than ever before, thanks to advances in our understanding of food flavor. For most common foods we now know the key odorants, so we know what to measure. Individual foods have (only) up to around 30 key odorants; and with sensitive, modern GC-MS systems, they can be targeted and analyzed rather easily. Around 10 years ago, a meta-analysis of food flavors demonstrated that if you analyze hundreds of foods for their main odorants, you only find 226 compounds (1). Apparently, there is a massive overlap in the key odorants of even very different foods and only 226 compounds describe the entire aroma space. This led us to the idea for a multi-targeted method that measures these 226 compounds. But this is not without challenges: these 226 compounds are present amidst thousands of other volatile compounds. Moreover, odor intensities can be very different meaning that there can be 10 orders of magnitude difference in the concentrations at which they are relevant.

It is only thanks to very recent developments in chromatography-MS systems, in particular the much-improved peak capacity and sensitivity, that we can now think about quantifying 226 compounds in one run. With this targeted 226 compounds analysis, we cover the entire aroma space, so we have all the information to correlate compounds to a product's flavor. The improved peak capacity of modern systems helps to avoid overlap and incorrect data. Those compounds that correlate with the off-flavor intensity, color, instability, and so on could potentially be relevant. But one should always carefully evaluate whether there is a true causal relationship, and what the underlying explanation is. Did you know that there is a perfect correlation between ice-cream sales and people drowning in the sea? This one is obvious, but in flavor-composition correlations that is not always the case.

Performing measurements is probably the simplest part of the job as an analytical chemist. What's difficult is deciding what to measure, and how to measure it. As is setting up the system and making sure it provides reliable data. Measuring everything using just one generic system is a safer approach. There is no risk of measuring the wrong compounds, you are sure the system works, no start-up issues, no expected errors, and so on. But zooming out too much holds the risk of missing the detail. Finding the right balance between hypothesis-driven testing and exploratory learning is what makes the task challenging. And we work in an environment where methods and instruments are getting more complex, numbers of people are getting fewer and experience is undervalued because information is everywhere. In our lab, we solve this by running every new sample on the broadest sample prep technique we have: arrow solid phase microextraction on a mixed fiber. For the separation, we use the GC-MS system with the highest peak capacity and best sensitivity, comprehensive GC×GC-ToF MS. This together gives us the broadest possible compound coverage with the best possible resolution and sensitivity. And, as a result, the best chance of a first-time-right approach.

Full article and references available online

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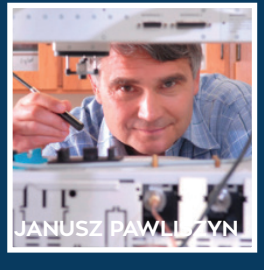

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SPECTROSCOPY

SORS and the Power of Light in Pharma

Understanding the role of spatially offset Raman spectroscopy in identifying counterfeit medicines, and more

Spatially offset Raman spectroscopy (SORS) has expanded the boundaries of traditional Raman analysis. Developed at the Science and Technology Facilities Council (STFC) Central Laser Facility, SORS allows for detailed chemical analysis of opaque or layered materials, including powders, coated tablets, and even products within sealed containers – making it a valuable tool for raw material verification, detection of counterfeit medicines, among other uses.

Pavel Matousek, one of the key figures behind SORS, co-founded Cobalt Light Systems through STFC to commercialize this technology. Rob Stokes joined in 2013, and then the company was acquired by Agilent Technologies in 2017, which helped bring SORS to a wider customer base.

Here, Matousek (STFC Senior Fellow at the Central Laser Facility) and Stokes (Director, Raman Spectroscopy at Agilent) share insights into how SORS has evolved and its applications in pharma.

What is SORS? And how does it expand the applications of Raman spectroscopy?

Pavel Matousek: SORS addresses a limitation of conventional Raman spectroscopy. If you have a dense powder or opaque object, traditional Raman can only analyze the surface – not what's deeper within. For instance, if you have a tablet with multiple layers, you might only be able to analyze the outer coating. Similarly, if the product is inside a container, then you will only be able to analyze the container.

SORS probes beyond the surface and can even analyze contents inside opaque containers. It was developed somewhat accidentally in the 2000s as part of a set of ultrafast laser experiments we were conducting at STFC's Central Laser Facility. Initially, these unexpected results were a nuisance in our trials! But when we investigated further, we realized that the phenomenon could allow us to chemically analyze materials beneath surfaces. By capturing Raman signals at different offsets from the laser illumination point, SORS can isolate information from various depths within a sample.

We formed Cobalt Light Systems to develop the technology into practical instruments that could be used in the real world.

Rob Stokes: The first impactful application of SORS in pharma was a mobile system called RapID, which was about the size of R2D2 from Star Wars. It had a handheld component that can be used to quickly verify the contents of containers; for example, allowing pharma companies to check incoming raw materials, without needing to open containers and/or packaging. These systems are still in use today!

From there, we expanded into other applications, including security and detection. This led to use cases in customs and border protection, which brings us back to pharmaceuticals in the form of counterfeit medicines.

How can SORS be used to detect counterfeit medicines?

RS: This is all in the research stage and it's all about pushing the limits of SORS. It lends itself very well to liquid medicines. We were already thinking about looking into the analysis of counterfeits – and our work happened to be coincident with that of another group of academics.

PM: At the start of the COVID-19 pandemic, Prof. Paul Newton from the Medicine Quality Research Group at Oxford University contacted us and we ended up having a socially distanced meeting in a park in Oxford! He was wondering whether the technology we had developed could be harnessed and translated to probe unopened vaccine vials in the field. We were a little skeptical because these are very challenging formulations with very low concentration formulations. We did some experiments that ultimately were very successful. All of this demonstrates the important nature of industry collaborating with national laboratories and academia. This work is really pushing the boundaries of what the technology can achieve; it's exciting to see how far we can take this.

The technology is now being trialled in other areas in partnership with Prof Newton's team, such as checking cough medicines.

What high impact stories can you share?

RS: There have been instances where we intercepted highly dangerous substances at borders using our handheld Raman systems. Some of these substances are unregulated, but incredibly harmful. With the internet fueling the popularity of these kinds of dangerous substances, it's invaluable to detect them early. We've intercepted signals at borders worldwide, identifying them as new or previously unknown threats, and then worked with local authorities to understand and respond appropriately. This capability of keeping harmful materials off the black market genuinely reduces potential harm.

Moments like these remind us how impactful our work can be.

RP-MS analysis of therapeutic oligonucleotides without the use of ion pair reagents

This application note based on the work of Hayashi and Sun (1) shows a non-IP-RP method for the analysis of therapeutic oligonucleotides using ammonium bicarbonate as mobile phase additive.

The method's applicability is proved by analysing various commercially available oligonucleotides with chemical modifications including six antisense oligonucleotides (ASO), three siRNA and four of their analogues. The oligonucleotides show sharp peaks, except for the phosphorothioated oligonucleotides like fomivirsen (Vitravene®) and mipomersen (Kynamro®) exhibiting much broader peaks. This is likely due to the presence of various stereoisomers. The analysis of lumasiran (Oxlumo®) in reconstituted plasma demonstrates the applicability of this method for bioanalyses.

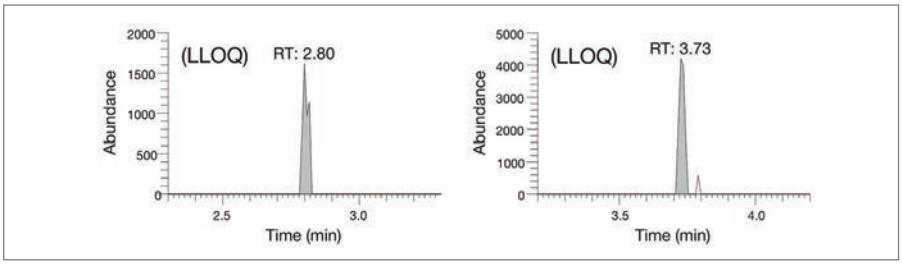

Fig. 1: Extracted ion chromatograms of the antisense (left) and sense (right) strands of lumasiran in the reconstituted plasma at the LLOQ [1].

The findings of this study indicate that this ammonium bicarbonate-based RP method is suitable for the bioanalysis of therapeutic oligonucleotides.

Full method details can be accessed here: https://ymc.eu/d/brDqy

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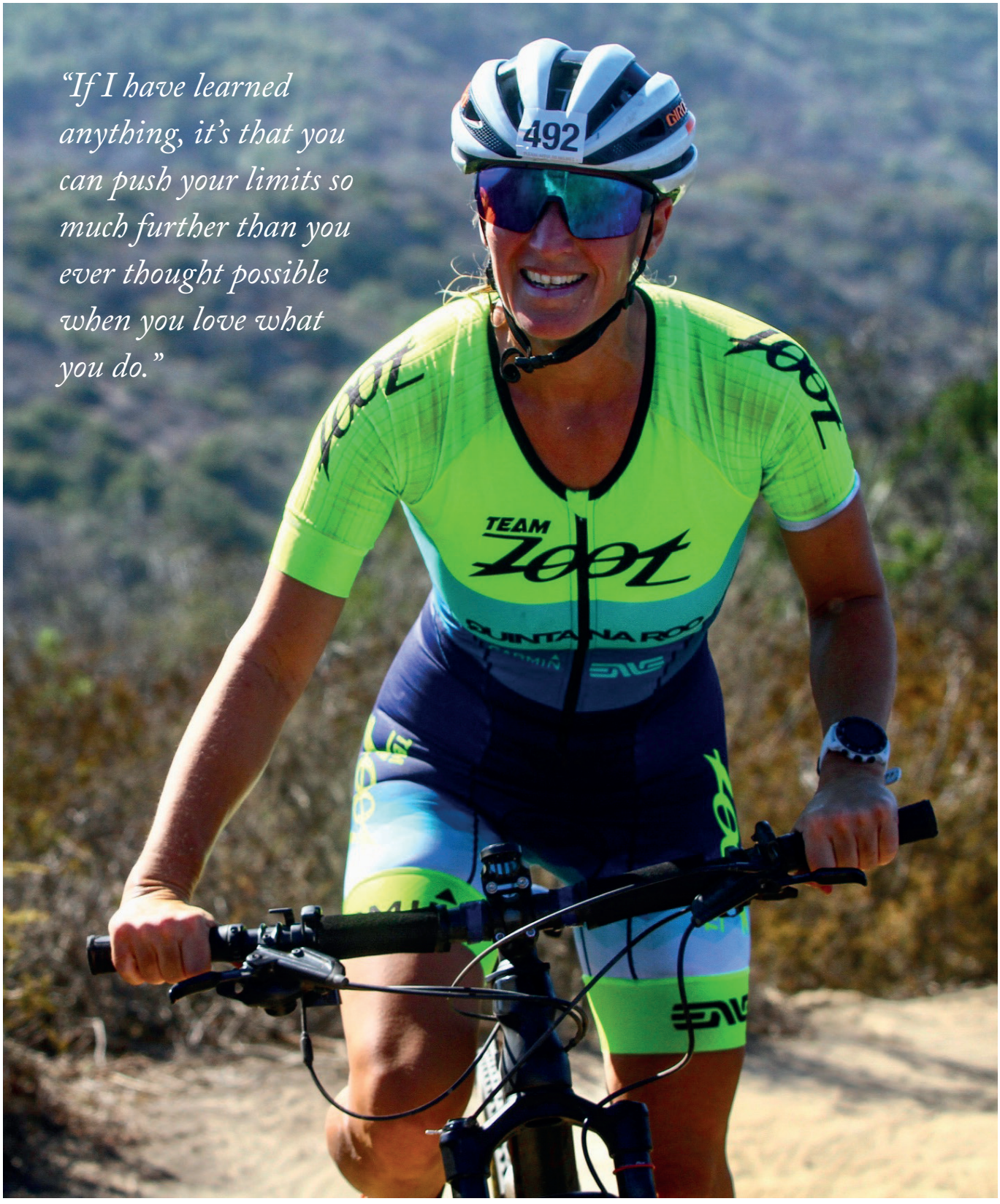
1. *Yoshiharu Hayashi and Yuchen Sun, Journal of the American Society for Mass Spectrometry Article ASAP, DOI: 10.1021/jasms.4c00270*



"If I have learned anything, it's that you can push your limits so much further than you ever thought possible when you love what you do."

A Voyage of Diagnostic Discovery

Sitting Down With…
Sandra Pankow, Founder & CEO, 3D BioAnalytiX

Did you always want to be a scientist?
As a kid growing up in a small village at the Baltic Sea in Northern Germany, I always thought I would one day sail the world. But I discovered that I really had a knack for the natural sciences and medicine, so I studied biology and biochemistry in Kiel, Germany. After obtaining my PhD in cell biology at ETH Zurich, Switzerland, I moved to the world-renowned John Yates laboratory at Scripps Research in California to follow my passion of developing novel proteomics methods that will lead to better diagnosis and treatment of devastating protein misfolding diseases, such as cystic fibrosis, amyloidosis, Alzheimer's, and other neurodegenerative disorders.

What led you to form 3D BioAnalytiX?
My work – and especially my discovery of a disease-specific protein interactome in cystic fibrosis, which was published in Nature in 2015 – inspired my team and I to understand what a misfolded protein – which presumably leads to disease specific interactions – really looks like in vivo. However, this wasn't possible with the molecular tools available at the time. We couldn't identify, let alone quantify, misfolded, aggregated proteins in patients.

And that's why I co-developed covalent protein painting (CPP) – a method that combines small, cell permeable, covalent labels with mass spectrometry – which allows us to identify and characterize misfolded proteins in vivo. In fact, it's not just misfolded proteins – we can characterize any protein conformational change across the whole proteome in an unbiased and, most importantly, quantitative manner.

To make use of these new techniques for drug development and diagnosis of misfolding diseases, I founded 3D BioAnalytiX in July 2023. Since then, I have further developed the method into a scalable and automatable platform, which has opened up a huge range of applications looking at conformational or structural change in the proteome. In addition, we developed a reagent kit to make the platform more accessible to others for drug development, which is now being used by the first, select customers. To be sure, developing and running a business has been a wild and challenging – but highly rewarding – ride. And I am looking very positively into the future – especially now that we have the first positive patient study results for a diagnostic blood test for amyloidosis.

Tell us more about the diagnostic test for amyloidosis…
While developing a blood test for neurodegeneration, we realized that we were able to detect and characterize the fold of TTR reliably in patient plasma and had a tool that could potentially address the underdiagnosis crisis in amyloidosis.

Together with Jeff Kelly and Mathew Maurer from the Amyloidosis Center at Columbia University, I ran a discovery study that showed that we can identify and distinguish ATTR patients from control patients from just 50 µl of plasma using our proteomics platform technology. We are now validating these results with many more patients and believe that we will have a blood-based diagnostic test soon that can for the first time directly identify and quantify the characteristic misfolded TTR aggregates in small amounts of plasma. Because of the scalability of the platform, it holds promise to become widely available and could help millions of patients – there are approximately 5.5 million patients in Europe and the US alone. We are extremely excited about the test and the results have been enthusiastically embraced by the amyloidosis community.

What's next for you and 3D BioAnalytix?
Personally, this journey is a huge adventure and, of course, it will be a huge risk to eventually focus and completely rely on the business. As a triathlete who has competed at the world level, I have never shied away from a good challenge though and, of course, we do have defined exit strategies. The next two milestones will be to i) grow the reagent kit business and include more selected customers, so that sales can support at least part of the business, and ii) and further develop our diagnostic blood tests. We were now awarded funding to do exactly that and are becoming part of the JLABS family, and I am very excited about that. The next bridge to cross will be securing further financing to grow 3D BioAnalytiX, and to hire the necessary scientists and bioinformaticians. We are working hard on that and I am grateful to all of those who believe in me – and especially my two little kids, who are firm believers that their mom will "slay" this!

Hold on, you're an elite triathlete!?
Yes, I am! I qualified for and participated in two world championships for cross-triathlon in 2022 and 2023 (XTERRA world championships in Italy) and didn't do too badly either (15th place in my age group). I was a huge sports nut as a kid, competed in gymnastics and won many swim and track competitions. I later learned to snowboard, surf, windsurf and sail, but it wasn't until late 2018 when a friend asked what the heck happened to me that I abandoned competitive sports! I soon found a triathlon to compete in and started training for it.

If I have learned anything, it's that you can push your limits so much further than you ever thought possible when you love what you do. But it is essential to keep your cool and persevere when the going gets tough. Of course, starting a new company can seem just like a triathlon at times…

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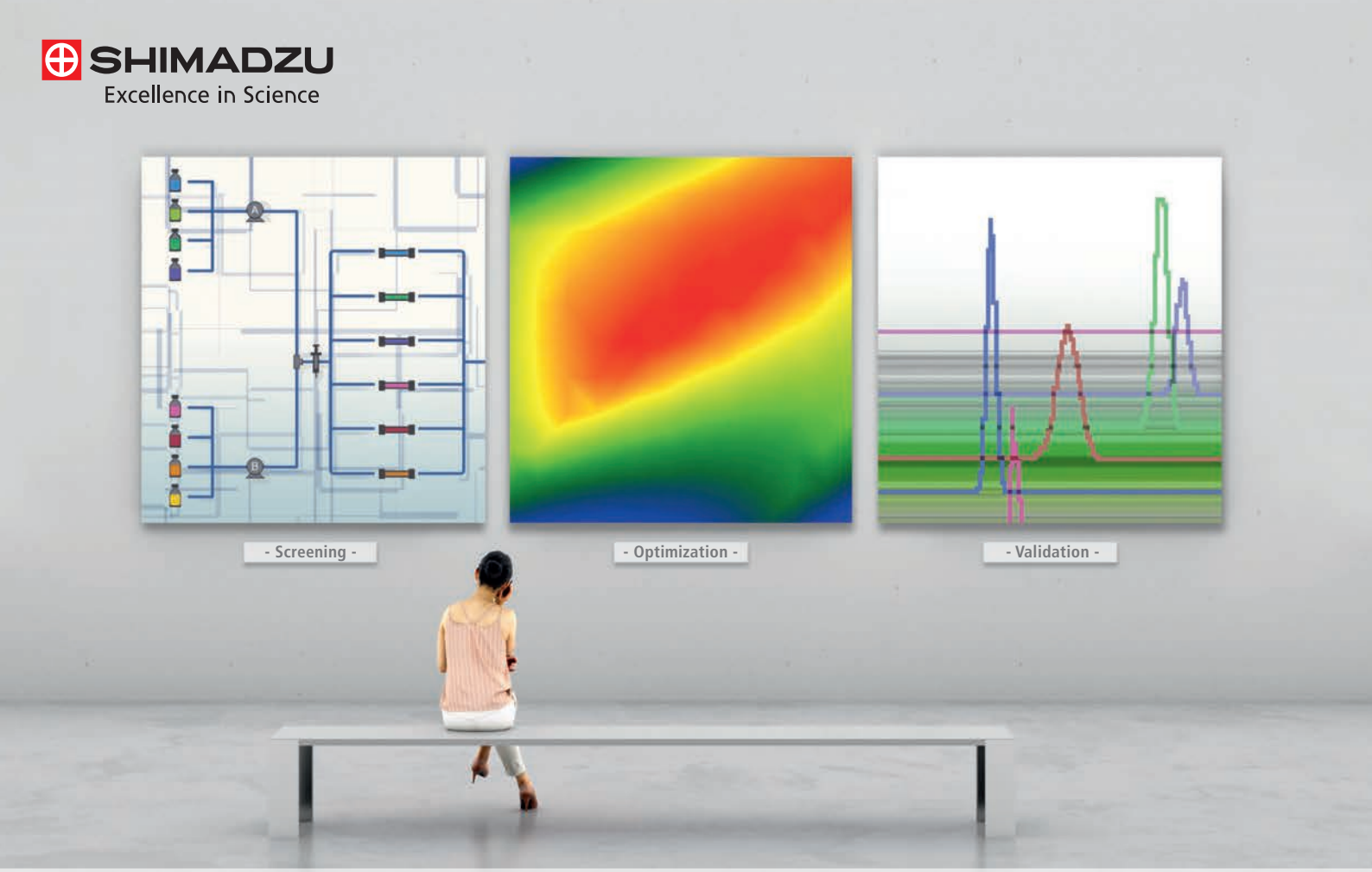

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